Arene–Amine Coupling

Highly Reactive, General, and Long-Lived Catalysts for Coupling Heteroaryl and Aryl Chlorides with Primary Nitrogen Nucleophiles**

*Qilong Shen, Shashank Shekhar, James P. Stambuli, and John F. Hartwig**

During the past decade, the palladium-catalyzed amination of aryl halides has become a principal method to form the C–N bonds of aromatic amines.[1–4] Although current catalysts are capable of coupling a wide range of amines with aryl halides, reactions with these catalysts have several limitations: the catalysts have short lifetimes in the reactions of primary amines with chloroarenes, even when conducted with the most recently developed, highly active catalysts containing basic, hindered alkylmonophosphines;[5–15] the reactions of primary alkyl amines with heteroaryl chloride reagents, which are important for the synthesis of biologically active molecules, have limited scope and require large amounts of catalyst;[7,8,11,13,15–20] and the reactions of primary alkyl amines with chloroarenes that possess common protic functional groups have not been described.

We now report on catalysts that can overcome these limitations. Our approach, which is based upon the selection of ligands that combine steric hindrance, strong electron donation, and tight chelation, leads to a catalyst that simultaneously possesses long lifetimes and displays high activity for reactions of primary nitrogen nucleophiles with chloropyridines. Many of the reactions occur with part-per-million quantities of catalyst and with turnover numbers that exceed those of previous catalysts by two or more orders of magnitude.

To identify the factors that would improve catalyst lifetime over that of current catalysts, we studied the reactions of primary amines and pyridine with aryl palladium(II) halide complexes and bisphosphine palladium(0) complexes bearing a basic, hindered alkyl monophosphine.[21–23] Addition of benzylamine or pyridine (py) to the palladium(0) complex $[Pd(PtBu_3)_2]$ led to no reaction [Eq. (1)]. However, addition of benzylamine or pyridine to the aryl palladium(II) halide complex $[Pd(PtBu_3)(Ar)(Br)]$ (Ar = *o*-Tol, Ph) displaced the

$$tBu_3P{-}Pd{-}PtBu_3 \; + \; py \rightarrow \text{no reaction} \qquad (1)$$

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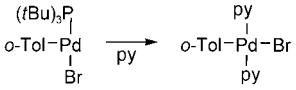
phosphine to form the free ligand and $[Pd(PhCH_2NH_2)_2(Ph)Br]$[24] or $[Pd(py)_2(o\text{-Tol})Br]$ [Eq. (2)].[25] Although displacement of hindered aromatic phosphines occurs from aryl palladium(II) complexes,[24,25] the



(2)

greater basicity of alkyl phosphines should make complexes of these ligands more stable toward displacement by amines and pyridines. Apparently, the higher basicity does not increase the strength of the bond between palladium(II) and a hindered alkyl phosphine enough to prevent displacement by the less hindered nitrogen donors. Displacement of the ligand from palladium accounts for the slow reactions of primary amines and pyridines because amine and pyridine complexes do not catalyze the amination of aryl chlorides.

To prevent displacement of the phosphine ligand, while maintaining the steric and electronic properties of the hindered alkyl monophosphines, we evaluated complexes containing hindered alkyl bisphosphines as catalysts for the coupling of primary amines with heteroaryl and aryl chlorides. A series of possible structures of palladium(0) complexes of chelating phosphines are summarized in Figure 1. The unsaturated (chelate)Pd^0 fragment adds aryl halides[26] and

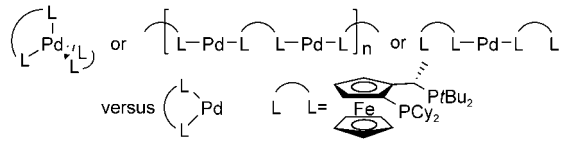
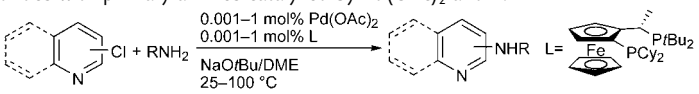
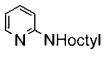
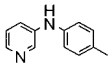
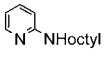
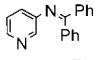
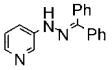
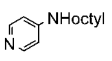
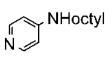
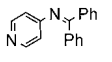
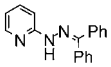
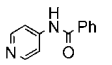
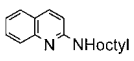
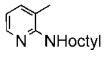
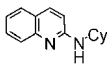
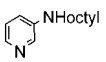
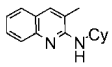
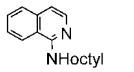
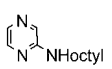
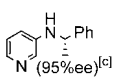


Figure 1. Potential structures of Pd^0 complexes with bisphosphine ligands and the Josiphos ligand L employed in this study. Cy = cyclohexyl.

Table 1: Coupling of heteroaryl chlorides with primary amines catalyzed by $Pd(OAc)_2$ and L.[a]



Entry	Product	Cat. [mol%]	Cond.	Yield [%][b]	Entry	Product	Cat. [mol%]	Cond.	Yield [%][b]
1		1.0	25 °C, 5 h	99	15		1.0	90 °C, 12 h	85
2		0.001	100 °C, 48 h	86	16		1.0	70 °C, 16 h	85
3		0.005	70 °C, 16 h	89	17		1.0	70 °C, 16 h	99
4		0.01	70 °C, 12 h	98	18		1.0	70 °C, 8 h	93
5		1.0	70 °C, 16 h	73	19		0.01	90 °C, 24 h	83
6		1.0	70 °C, 16 h	92	20		1.0	70 °C, 10 h	99
7		1.0	70 °C, 16 h	99	21		1.0	70 °C, 24 h	75
8		1.0	70 °C, 18 h	99	22		0.005	90 °C, 48 h	94
9		0.005	90 °C, 30 h	96	23		0.01	100 °C, 48 h	60
10		0.005	70 °C, 24 h	93	24		0.001	100 °C, 48 h	89
11		0.01	100 °C, 24 h	95	25		0.005	90 °C, 15 h	91
12		0.01	100 °C, 48 h	90	26		0.005	100 °C, 16 h	82
13		0.01	100 °C, 48 h	79	27		0.05	100 °C, 24 h	91
14		1.0	70 °C, 16 h	67					

[a] Reactions conducted with a 1:1 ratio of metal to ligand, 1 mmol ArCl, 1.2 equiv amine, and 1.4 equiv NaO*t*Bu in 1 mL 1,2-dimethoxyethane (DME). [b] Yield after isolation. [c] From (1-phenylethyl)amine that is stated to be 99% *ee*.

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must be readily generated for high reactivity. Many bisphosphines form $(chelate)_2Pd$ complexes that slowly dissociate their ligands. Because this dissociation precedes oxidative addition, these complexes tend to add aryl halides slowly.[27] Others, such as 1,1′-ferrocenylphosphines, are flexible enough to adopt conformations that link two metals, or possess κ^1 coordination modes.[28] Ligands that adopt κ^1 coordination modes will be more easily displaced by amines and pyridines than those that adopt chelating structures. Thus, we selected hindered alkyl bisphosphines with rigid backbones to disfavor formation of stable $(chelate)_2Pd^0$ complexes containing two bidentate ligands, to disfavor formation of complexes with κ^1 structures, and to favor generation of the $(chelate)Pd^0$ fragment.[29]

The Josiphos ligand with one di-*tert*-butylphosphanyl and one dicyclohexylphosphanyl group shown in Figure 1[30] is now commercially available, but has rarely been used successfully in catalytic chemistry. It is air-stable, both as a solid and in solution for at least 24 h, as determined by ^1H NMR and ^{31}P NMR spectroscopy. The combination of the severe steric hindrance, conformational preferences of the backbone, and recent success in generating catalysts for the coupling of aryl tosylates[31,32] led us to study complexes of this ligand as catalysts for the amination of heteroaryl and aryl chlorides.

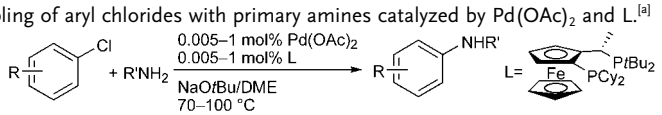
Reactions of heteroaryl chlorides with primary nitrogen nucleophiles catalyzed by a combination of this Josiphos ligand and $Pd(OAc)_2$ are summarized in Table 1. Catalysts generated from $Pd(OAc)_2$ were more reactive than those generated from $[Pd(dba)_2]$. Pyridyl chlorides bearing the halogen in the 2-, 3-, or 4-position underwent reaction with a variety of primary amines and related nucleophiles in high yield at room temperature or with mild heating. In contrast, similar reactions in the presence of catalysts with hindered monodentate or aromatic bisphosphine ligands were conducted with high catalyst loadings or at high temperatures. Not only reactions of pyridyl chlorides, but reactions of quinolinyl, isoquinolinyl, and pyrazyl chlorides, occurred under mild conditions (Table 1, entries 22–26).

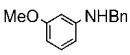
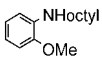
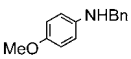
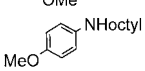
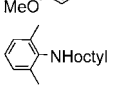
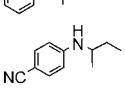
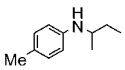
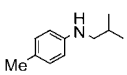
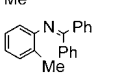
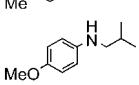
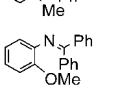
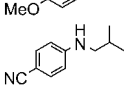
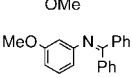
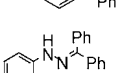
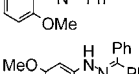
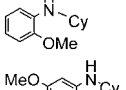
Reactions without catalyst were conducted in parallel with the catalyzed ones. Only reactions of quinolines and isoquinolines generated any measurable quantity of products, and conversions were below 40% in these cases. Reactions of 2- and 4-chloropyridines occur more readily in polar solvents or under high pressure but are typically conducted at temperatures closer to 150 °C.[33] Nucleophilic substitution of 3-chloropyridines is often by a factor of 10^4 to 10^5 slower than that of 2- and 4-chloropyridines.[34]

Besides the generality of the reaction, the turnover numbers are remarkable. High yields were observed for reactions between pyridyl chlorides and unhindered primary amines with loadings of metal salt and ligand between 10 and 50 ppm (Table 1, entries 2, 3, 9, 10, 22, 24–26). Some previous reactions of chloropyridines with low loadings of palladium were conducted with high loadings of ligand.[15] This is misleading because the ligand is typically more expensive than the metal.

Hindered primary amines, such as *tert*-butylamine, as well as benzophenone hydrazone and benzophenone imine, also reacted in high yields with chloropyridines (Table 1, entries 5–7, 14, 16, 17, 20). These reactions required more catalyst, although the loading remained at or below 1 mol%. The more hindered 2-chloro-3-methylpyridine also reacted with octylamine in high yield (Table 1, entry 9). Even benzamide reacted with 2- and 4-chloropyridine with this catalyst (entries 8, 21). No coupling of amides with a pyridyl chloride has previously been reported with any catalyst. No products from coupling of primary nitrogen nucleophiles with heteroaryl chlorides to form di-heteroaryl amines were observed in any case by GC/MS.

Table 2: Coupling of aryl chlorides with primary amines catalyzed by $Pd(OAc)_2$ and L.[a]



Entry	Product	Cat. [mol%]	Cond.	Yield [%][b]	Entry	Product	Cat. [mol%]	Cond.	Yield [%][b]
1		0.005	90 °C, 48 h	94	13		0.005	100 °C, 48 h	99
2		0.01	100 °C, 48 h	98	14		0.005	80 °C, 20–24 h	98
3		0.05	100 °C, 48 h	93	15		0.1	100 °C, 48 h	90
4		0.1	100 °C, 48 h[c]	92	16		0.05	100 °C, 48 h	99
5		0.1	100 °C, 36 h	97	17		0.01	80 °C, 20–24 h	87
6		0.05	100 °C, 48 h	92	18		0.1	100 °C, 48 h	82
7		0.05	100 °C, 48 h	83	19		1.0	80 °C, 20–24 h	61
8		1.0	100 °C, 18–24 h	94	20		1.0	80 °C, 20–24 h	77
9		0.005	80 °C, 20–24 h	99	21		1.0	80 °C, 20–24 h	86
10		0.05	100 °C, 48 h	99	22		1.0	100 °C, 18–24 h	87
11		0.5	100 °C, 36 h	99	23		1.0	80 °C, 20–24 h	82
12		0.01	100 °C, 18–24 h	68					

[a] Reactions conducted with a 1:1 ratio of metal to ligand, 1 mmol ArCl, 1.2 equiv amine, and 1.4 equiv NaO*t*Bu in 1 mL DME. [b] Yield after isolation. [c] 3.0 equiv of octylamine used.

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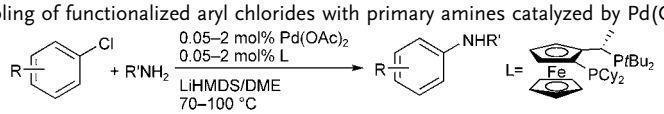
The turnover numbers of 86000, 18600, and 8300 for the reactions of 2-, 3- and 4-chloropyridine with octylamine are an order of magnitude higher than those for reactions of any amine with the corresponding bromopyridine[29,35] and about two orders of magnitude higher than those for reactions of any amine with the chloropyridine,[7,8] and the value of 86000 is nearly three orders of magnitude greater than those reported for the reaction of a pyridyl chloride with any primary amine.[8] To achieve such high turnover numbers with equal amounts of ligand and palladium, we mixed the dilute solutions of $Pd(OAc)_2$ and ligand before adding the amine or heterocyclic substrate. Presumably the combination of amine and base leads to the reduction of palladium(II) to palladium(0).

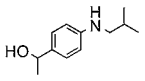
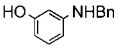
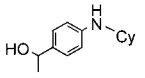
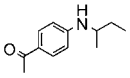
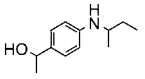
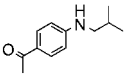
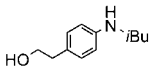
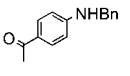
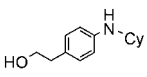
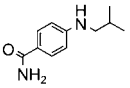
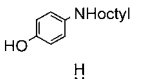
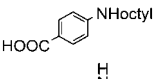
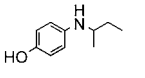
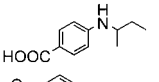
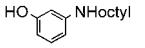
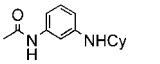
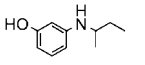
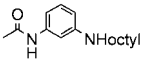
These high activities in reactions of chloropyridines led us to perform reactions of chloroarenes using the same catalyst. Results (displayed in Table 2) show similarly high yields with low catalyst loadings. Reaction of octylamine with chlorobenzene occurred to completion in 48 h and formed the coupled product in 94% yield at 90°C, with only 50 ppm of catalyst (entry 1). This yield under these conditions corresponds to a turnover number of 18800. This value exceeds the maximum turnover numbers achieved previously for the reaction of an aryl chloride with any amine by nearly an order of magnitude and the maximum turnover numbers for the reaction of a primary alkyl amine by nearly two orders of magnitude. Reactions of several other combinations of primary amines and chloroarenes (entries 9, 13, 14) occurred in similarly high yields with the same amount of catalyst. The reactions of α-branched primary amines, for example, the reaction of cyclohexylamine with chlorobenzene, required more catalyst, but occurred in high yield with only 0.05 mol% palladium (TON = 1980, Table 2, entry 10). This loading of catalyst is more than an order of magnitude lower than that of previous reactions of α-branched primary amines with chloroarenes.[8] In addition, reactions of *sec*-butylamine occurred in high yield with 0.01–1 mol% catalyst (entries 16–18). Reactions of benzophenone hydrazone and benzophenone imine occurred in high yield with 1.0 mol% catalyst (entries 19–23). Catalyst loadings have not yet been optimized with these reagents. Products from diarylation were observed by GC/MS only for the reaction of octylamine with 4-chloroanisole.[36]

One benefit of the palladium-catalyzed route to *N*-aryl amines is the high tolerance of the reaction for functional groups.[37–41] Our results (Table 3) show that catalysts containing the hindered Josiphos ligand extend the scope of the reactions of functionalized substrates to include the coupling of primary amines with chloroarenes bearing protic functionality. This catalyst system is less reactive with weak bases than those generated from monodentate ligands.[9,10,21,38,42] However, complexes of this Josiphos ligand catalyze reactions of primary amines with chloroarenes possessing a free alcohol, phenol, carboxylic acid, amide, or enolizable ketone functionality in high yields with LHMDS (= $LiN(SiMe_3)_2$) as base.[40,41] Reactions of primary alkyl amines with aryl chlorides possessing related functional groups were previously limited to electron-poor aryl chlorides containing an ester functionality.[9,42] No examples of reactions of primary amines with chloroarenes containing the functional groups of the substrates collected in Table 3 have been published previously.

Thus far, no single combination of metal and ligand generates the most reactive catalyst for coupling of all types of amines and aryl halides. The strengths of the catalyst reported here complement those of previously reported catalysts that contain hindered monodentate ligands. The former is less, the latter more reactive toward secondary than toward primary amines. The high reactivity of catalysts containing the hindered bis(dialkyl) phosphanyl Josiphos ligand L results

Table 3: Coupling of functionalized aryl chlorides with primary amines catalyzed by $Pd(OAc)_2$ and L.[a]



Entry	Product	Cat. [mol%]	Cond.	Yield [%][b]	Entry	Product	Cat. [mol%]	Cond.	Yield [%][b]
1		0.5	100°C, 18 h	90	10		0.5	100°C, 20 h	84
2		0.5	100°C, 20 h	70	11		0.5	70°C, 20 h	87
3		0.5	100°C, 18 h	83	12		0.5	70°C, 20 h	92
4		0.5	100°C, 20 h	87	13		0.5	70°C, 20 h	69
5		0.5	100°C, 20 h	86	14		0.5	100°C, 20 h	67
6		2.0	100°C, 18 h	72	15		0.05	100°C, 20 h	81
7		2.0	100°C, 20 h	66	16		0.05	100°C, 24 h	85
8		0.5	100°C, 18 h	85	17		0.05	100°C, 24 h	74
9		0.5	100°C, 20 h	67	18		0.05	100°C, 20 h	99

[a] Reactions conducted with a 1:1 ratio of metal to ligand, 1.0 mmol ArCl, 1.2 equiv amine, and 2.4 equiv LHMDS in 1 mL DME. [b] Yield after isolation.

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from the combination of steric hindrance, strong electron donation, and tight chelation.

Experimental Section

Representative procedures: Procedure without a glovebox (Table 1, entry 2): A stock solution (100 μL) containing $Pd(OAc)_2$ (1×10^{-3} mmol) and CyPF(*t*Bu) (1×10^{-3} mmol) was added to a 4-mL vial containing 2-chloropyridine (0.114 g, 1.00 mmol) and NaO*t*Bu (0.135 g, 1.40 mmol) in 1.0 mL of DME. Octylamine (0.155 g, 1.20 mmol) was then added by syringe. The vial was sealed with a cap containing a PTFE septum, and the reaction mixture was stirred at 100 °C until the 2-chloropyridine was consumed, as determined by gas chromatography. The reaction solution was adsorbed directly onto silica gel, and the product was isolated by eluting with hexane/ethyl acetate (85:15) to give 3-(*N*-octylamino)pyridine as a yellow solid (178.1 mg, 86 % yield).

Procedure with a glovebox (Table 1, entry 1): An oven-dried resealable Schlenk flask capped with a rubber septum was evacuated and backfilled with N_2. To the flask was added NaO*t*Bu (0.135 g, 1.40 mmol) and a stirring bar. The flask was evacuated and backfilled with N_2 three times. To the flask was then added 3-chloropyridine (0.114 g, 1.00 mmol, 95.0 μL), DME (1.0 mL), a stock solution (5.0 μL) containing $Pd(OAc)_2$ (5.0×10^{-5} mmol) and L (5.0×10^{-5} mmol), and octylamine (0.155 g, 1.20 mmol). The rubber septum was wrapped with vinyl electrical tape to prevent leaking. The resulting mixture was stirred for 48 h at 100 °C until the 3-chloropyridine was consumed, as determined by gas chromatography. The reaction solution was adsorbed directly onto silica gel, and the product was isolated by eluting with hexane/ethyl acetate (85:15) to give 204.3 mg (99 %) of 3-(*N*-octylamino)pyridine as a yellow solid.

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